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Green Synthesis of Biologically Significant Pyrano and Pyrido Pyrimidine Derivatives: A Review

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Abstract: ***Pyrimidine derivatives are an important class of heterocyclic compounds known for their diverse biological activities, such as anticancer, antiviral, antibacterial, and antifungal properties. The synthesis of these compounds traditionally involves the use of toxic chemicals and harsh reaction conditions, which are detrimental to both the environment and human health. In recent years, green chemistry approaches have emerged as viable alternatives to conventional methods. This review summarizes recent advances in environmentally benign synthetic strategies for pyrano and pyrido pyrimidine derivatives with established pharmacological relevance. The analysis focuses on solvent free reactions, green catalysts, microwave and ultrasound assisted methodologies, and multicomponent protocols reported in contemporary literature. Comparative assessment indicates that non-conventional activation techniques significantly reduce reaction time and environmental burden while improving yields and selectivity. The review highlights mechanistic trends and identifies research gaps in scalable sustainable synthesis for drug discovery. These findings support the continued integration of green chemistry principles in heterocyclic medicinal chemistry.***

Keywords: Microwave assisted synthesis, ultrasound assisted synthesis, multicomponent reactions, heterocyclic medicinal chemistry and green catalysis.

1. Introduction

Genetic materials are composed of heterocycles such as adenine, guanine, cytosine, thymine, and uracil. Nitrogen-containing six-membered heterocycles and their fused derivatives, like pyrano/pyridopyrimidines, have been reported to exhibit a broad range of biological activities. These include antiallergic [1], antibacterial [2], anti-inflammatory, analgesic [3], antitumour [4], antileishmanial [5], tuberculostatic [6], antimicrobial [7], tyrosine kinase [8], anticonvulsant [9], antihypertensive [10] activities.

The synthesis of fused pyrimidines is of considerable interest for creating biodynamic heterosystems. This approach has proven to be both attractive and valuable in designing new molecular frameworks for potential drugs with diverse pharmacological activities. Pyrimidine-containing molecules are an ever-expanding focus of research in heteroaromatic chemistry due to their unique structures, which offer numerous applications in pharmaceutical and agrochemical research, as well as, more recently, in materials science**.** Pyrimidine (Fig. 1) is the parent ring structure of a variety of compounds that play crucial roles in biological processes. This structural design is also a core component of many pharmaceutical agents and naturally occurring substances, such as vitamins, coenzymes, purines, pterins, nucleotides, and nucleic acids. The properties of pyrimidines are largely determined by the electron-withdrawing characteristics of the two nitrogen atoms, which enhance each other's electronic effects at the 2-, 4-, and 6-positions. Pyrimidines are six-membered aromatic heterocyclic compounds with nitrogen at positions 1 and 3 of the ring. They are crucial building blocks for many bioactive molecules and play a vital role in cellular metabolism, being components of nucleic acids like DNA and RNA. Pyrimidine derivatives exhibit a wide spectrum of pharmacological activities, making them a central focus in medicinal chemistry.

Due to presence of vascular endothelial growth factor receptors, pyrimidine and fused pyrimidines are used as cancer therapy against various types of cancers as approved by the US Food and Drug Administration.[11,12] There are various examples of drugs that contain pyrimidine molecules as a core moiety used as anticancer agents .[13] By considering these recent findings, researchers are focusing on the synthesis of new fused bicyclic and tricyclic pyrimidine analogs and screening them against various cancer cell lines.[14,15]. However, traditional synthetic methods often involve the use of harmful reagents, solvents, and catalysts, which pose environmental and health risks. As a result, there has been an increasing demand for the development of sustainable, green synthetic routes that minimize environmental impact.

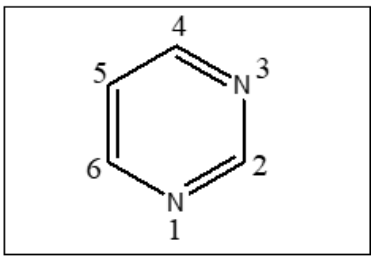


Figure 1: Pyrimidine

Green chemistry has become a major area of research in modern organic synthesis. The concept of "green chemistry" emerged in the early 1990s and is now widely applied to address fundamental scientific challenges related to protecting human health and the environment, while also achieving commercial feasibility. Nonclassical methods that follow the principles of green chemistry reduce or even

eliminate the production of hazardous substances, while also increasing product yield. Microwave (MW)-assisted organic synthesis has become one of the key green chemistry techniques in recent years. Its ability to rapidly synthesize organic compounds is particularly beneficial for library generation. Additionally, microwave assisted synthesis allows modifications in selectivity, solvent and catalyst free conditions.

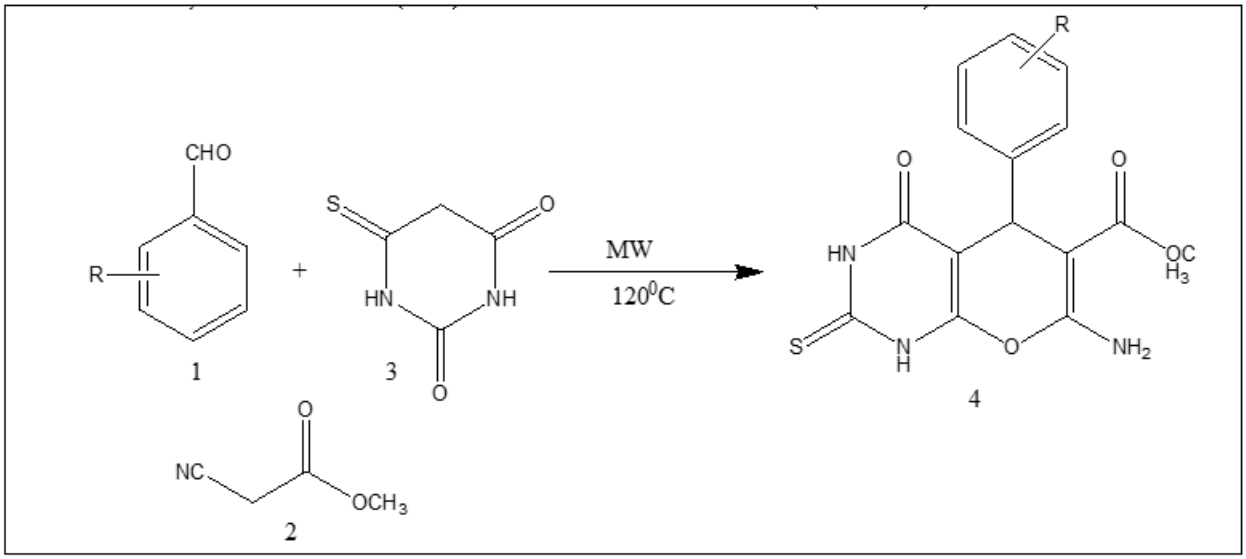
1) Microwave assisted synthesis

In the past few years, the synthesis of heterocyclic compounds has been pivotal in medicinal chemistry research, with numerous significant advancements in organic chemistry, including novel synthetic strategies, methods, and the development of a wide range of analytical techniques. As a result, modern chemists are no longer limited to using only thermal energy to drive chemical reactions. As the complexity of problems has increased and newer methods for activating chemical reactions have become available, chemists have turned to microwave techniques for the rapid and efficient synthesis of various compounds. This is due to the selective absorption of microwave energy by polar molecules. Microwave irradiation has been shown to enhance reaction rates, improve product yields in chemical synthesis, and facilitate the formation of a variety of carbon-heteroatom bonds.

Microwaves interact directly with the molecules in the entire reaction mixture, causing a rapid increase in temperature. Since this process is not limited by the thermal conductivity of the vessel, it leads to instantaneous localized superheating of any substance that responds to dipole rotation or ionic conductivity. Only the contents of the reaction vessel are heated, not the vessel itself, which allows for better homogeneity and selective heating of polar molecules. A wide variety of new chemistries can be achieved through microwave irradiation, with many recent synthetic applications demonstrating its potential. Despite the success in synthesizing numerous heterocyclic compounds and developing new, environmentally friendly processes, many microwave-assisted applications remain unexplored.

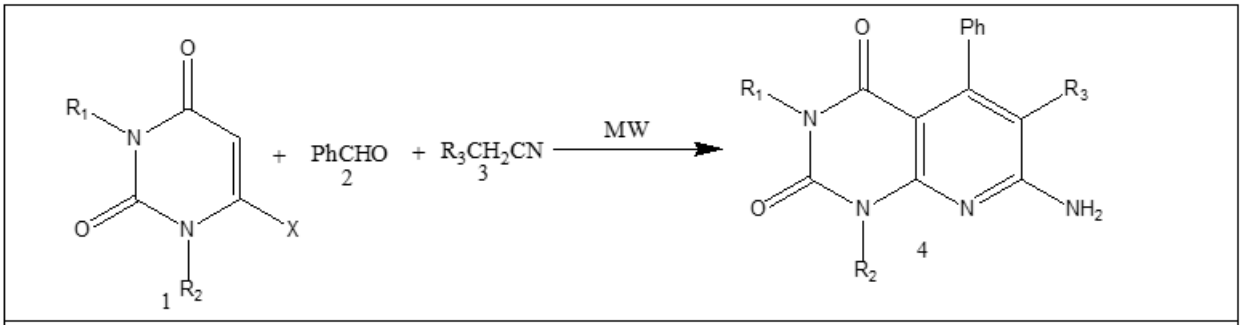
Below, we describe studies of microwave-assisted synthesis of N and O-type heterocyclic compounds reported in the literature.

Bhat et al. [16] reported the synthesis of pyrano[2,3-d]pyrimidinone derivatives **4** through a multicomponent reaction. This involved a solution of substituted aromatic aldehydes **1**, methyl cyanoacetate **2**, and thio-barbituric acid **3**, with water as the solvent, under microwave (MW) irradiation at 250 W and 120°C (Scheme 1).



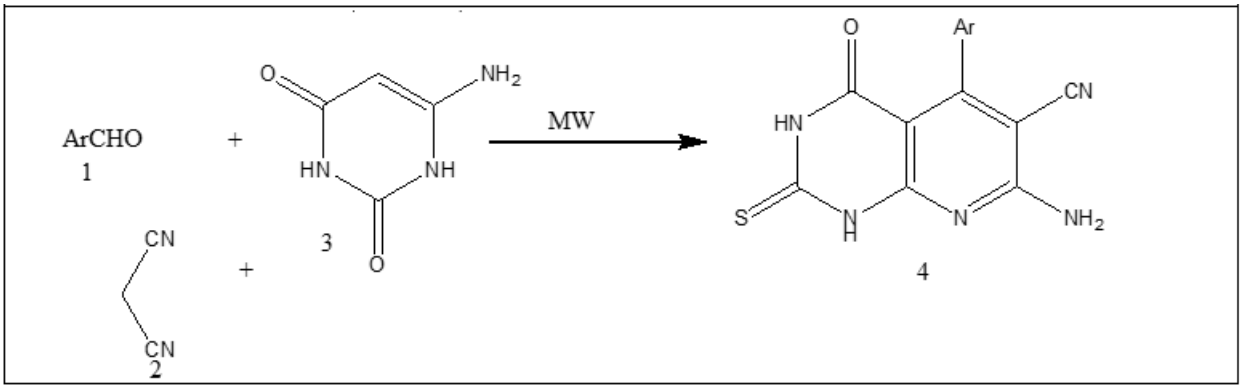
Scheme 1: Synthesis of pyrano[2,3-d]pyrimidinone derivatives

Ipsita et al. [17] reported a novel three-component, one-pot synthesis of pyrido[2,3-d]pyrimidines **4** under microwave irradiation at 60% power and 80°C for 4–5 minutes in the solid state. The reaction involves equimolar amounts of N,N-dimethyl barbituric acid **1**, benzaldehyde **2**, and malononitrile **3**, conducted without the use of a catalyst (Scheme 2).



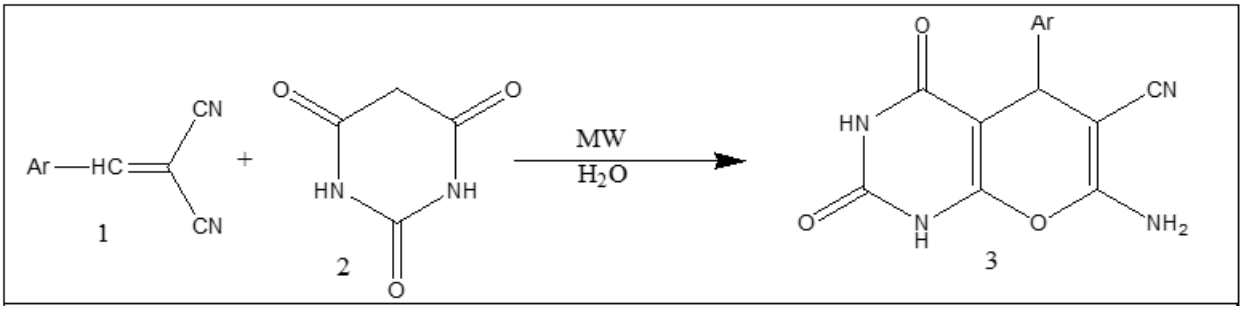
Scheme 2: One-pot synthesis of pyrido[2,3-d]pyrimidines

Shahrzad et al. [18] reported an efficient synthesis of pyrido[2,3-d]pyrimidine derivatives **4** through a one-pot, three-component reaction. This reaction involved aromatic aldehyde **1**, malononitrile **2**, and 4(6)-aminouracil **3**, conducted under microwave irradiation in aqueous media (Scheme 3).



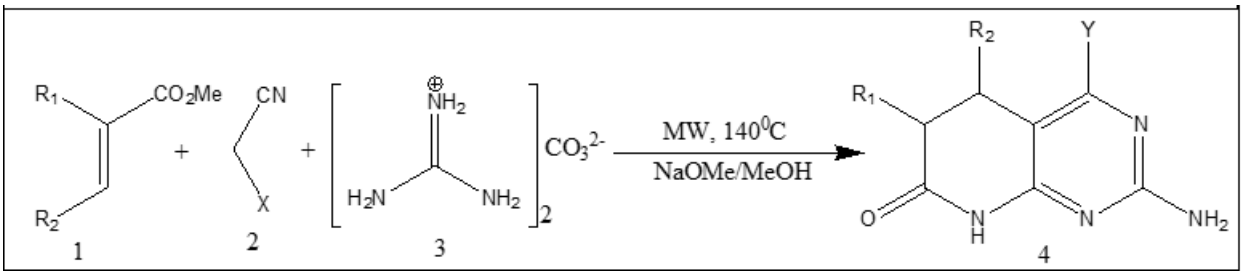
Scheme 3: Synthesis of pyrido[2,3-d]pyrimidine derivatives

Yuan et al. [19] successfully synthesized 7-amino-6-cyano-5-aryl-5H-pyrano[2,3-d]pyrimidine-2,4(1H,3H)-diones 3 under microwave irradiation. A dry 25 mL flask was charged with arylidene malononitrile **1**, barbituric acid **2**, and **3** mL of water. The flask was then connected to refluxing equipment and irradiated with microwave power at 285 W for 3–5 minutes (Scheme 4).



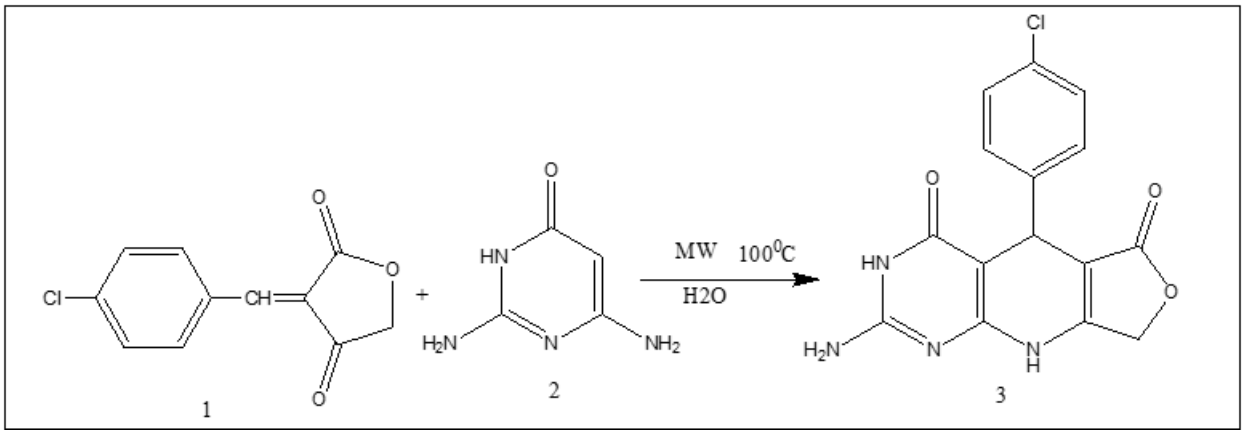
Scheme 4: Synthesis of 7-amino-6-cyano-5-aryl-5H-pyrano[2,3-d]pyrimidine-2,4(1H,3H)-diones

Mont et al. [20] synthesized functionalized pyrido[2,3-d]pyrimidines **4** via cyclocondensation of unsaturated esters **1**, active methylene compounds **2** (such as malononitrile or methyl cyanoacetate), and guanidinium carbonate **3** under microwave irradiation at 140°C (Scheme 5).



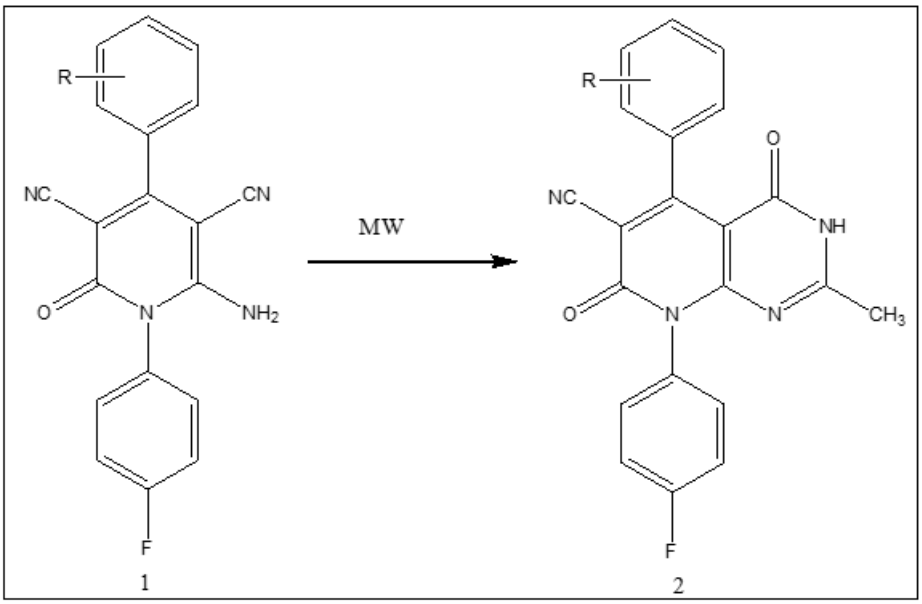
Scheme 5: Synthesis of pyrido[2,3-d] pyrimidines

Jiang et al. [21] also reported a simple synthesis of pyrido[2,3-d]pyrimidine derivatives **3** using 3-(4-chlorobenzylidene)furan-2, 4 (3H, 5H)-dione **1** and 2,6-diaminopyrimidine-4(3H)-one **2**, with water as the solvent, under microwave irradiation at 150 W and 100°C for a specified time (Scheme 6).



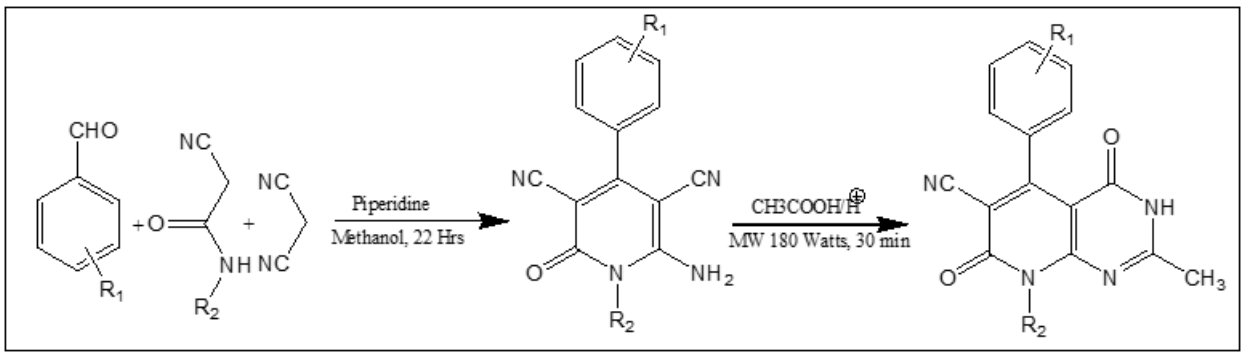
Scheme 6: Synthesis of pyrido [2, 3-d] pyrimidine derivatives

Kamlesh et al. [22] synthesized novel pyrido[2,3-d] pyrimidine derivatives **2** using 6-amino-1-(4-fluorophenyl)-2-oxo-4-phenyl-1,2-dihydro pyridine-3,5-dicarbonitrile derivatives **1** in acetic acid, which served as a self-solvent. A catalytic amount of concentrated sulfuric acid was added to promote the reaction. The reaction mixture was heated in an oil bath at reflux temperature, and the same reaction mixture was also monitored under microwave irradiation at 180 MW (Scheme 7).



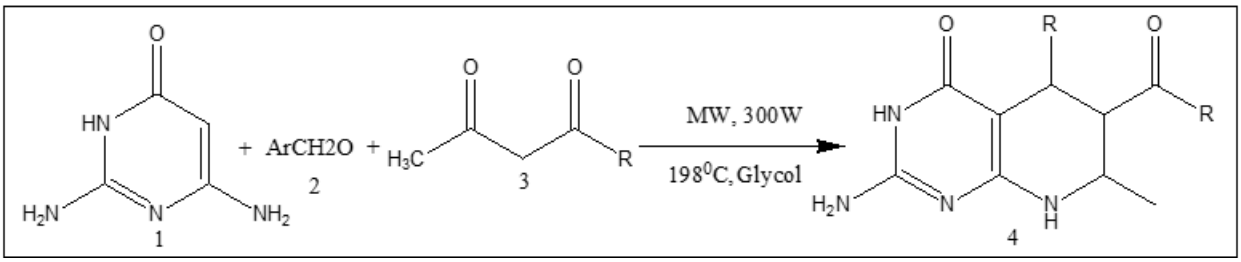
Scheme 7: Synthesis of pyrido[2, 3-d] pyrimidine derivatives

Kamlesh et al. [23] reported the microwave assisted synthesis of novel pyrido [2, 3-*d*] pyrimidines using dihydropyridines. The reaction mixture was subjected to MW at 180 W power (Scheme 8).



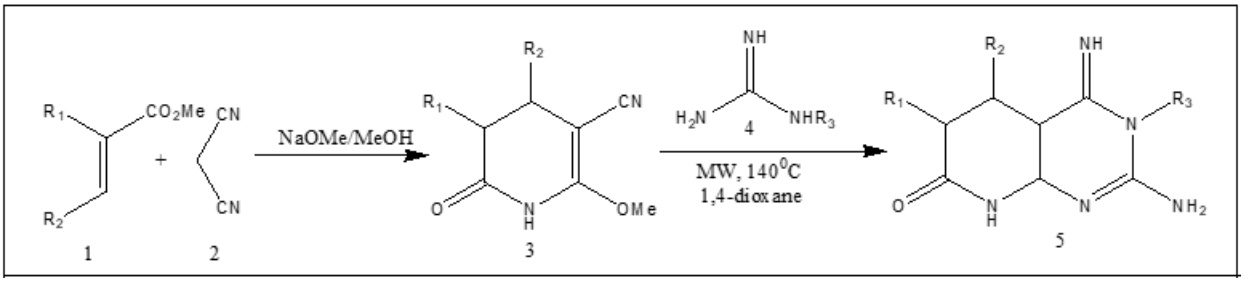
Scheme 8: Synthesis of pyrido[2,3-*d*]pyrimidines

Shujiang et al. [24] also reported the microwave-assisted one-pot synthesis of dihydropyrido[2,3-d]pyrimidine derivatives **4** using a mixture of 2,6-diaminopyrimidin-4-one **1**, aldehyde **2**, and 1,3-dicarbonyl compound **3** in glycol, without a catalyst, under microwave irradiation at 300 W power and 198°C for 4–7 minutes (Scheme 9).



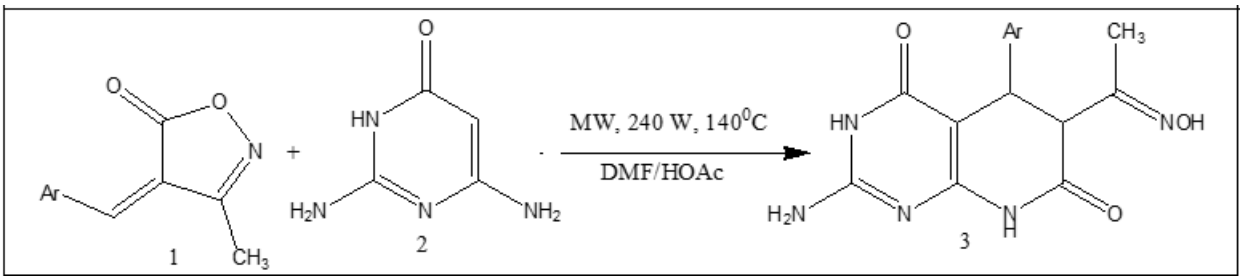
Scheme 9: Microwave-assisted one-pot synthesis of dihydropyrido[2,3-d]pyrimidine derivatives

Galve et al. [25] reported the synthesis of 2-arylamino substituted 4-amino-5,6-dihydropyrido[2,3-d] pyrimidin-7(8H)-ones **5** by treating pyridones **3** (synthesized from α, β-unsaturated esters **1** and malononitrile **2**) with aryl guanidines **4**, resulting in the formation of 3-aryl substituted pyridopyrimidines 5. These compounds undergo the Dimroth rearrangement in the presence of NaOMe/MeOH. The overall yields of this three-step protocol are higher than those obtained from the multicomponent reaction involving α, β-unsaturated ester 1, malononitrile 2, and aryl guanidine 4 (Scheme 10).



Scheme 10: Synthesis of 2-arylamino substituted 4-amino-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-ones

Shujiang et al. [26] developed an efficient method for synthesizing a new class of pyrido[2,3-d]pyrimidine derivatives **3**, using a reaction mixture of 4-arylidene-3-methylisoxazol-5(4H)-one **1**, 2,6-diaminopyrimidin-4(3H)-one **2**, DMF, and HOAc, under microwave irradiation at 240 W power and 140°C (Scheme 11).



Scheme 11: Synthesis of pyrido[2,3-d]pyrimidine derivatives

2) Use of Ultrasound

Ultrasound is widely used in organic chemistry, providing a versatile and efficient method for synthesizing a broad range of heterocycles. The study of ultrasound focuses on understanding how sound waves and their properties affect chemical systems. Ultrasound frequencies range from approximately 20 kHz to 10 MHz and can be divided into three main regions: low-frequency, high-power ultrasound (20–100 kHz), high-frequency, medium-power ultrasound (100 kHz–1 MHz), and high-frequency, low-power ultrasound (1–10 MHz). Ultrasound can be transmitted through any medium—solid, liquid, or gas- that has elastic properties. The movement of the sound source causes the particles in the medium to oscillate in the direction of the wave, generating both longitudinal and transverse waves.

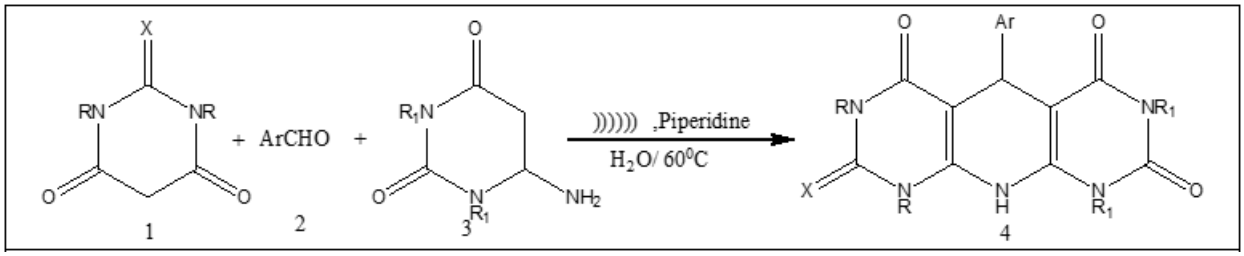
As the molecules vibrate, the average distance between them decreases during the compression cycle and increases during expansion. When the average distance exceeds the critical molecular distance required to maintain the liquid's integrity, the liquid breaks down, leading to the formation of cavities (cavitation) and bubbles. Cavitation refers to the formation, growth, and implosive collapse of bubbles within liquids, driven by sound. This process, a key factor in sonochemistry, occurs in various mediums such as water, organic solvents, biological fluids, liquid helium, molten metals, and others. The solvent or reagent vapor fragments, producing reactive species like free radicals or carbenes. These high-energy species concentrate at the bubble interface, leading to intermolecular reactions. Non-volatile solutes can also accumulate at the interface and react with these high-energy species. Additionally, the shock waves produced by bubble collapse can impact reactivity by altering the solvation of reactive species. Many common reactions in synthetic heterocyclic chemistry have been carried out more efficiently using ultrasound techniques.

There are several advantages of use of ultrasound. Typically, it leads to increased yields and a reduction in by-products. Reactions occur more quickly, allowing for lower

temperatures to be used. Ultrasound provides alternative reaction pathways due to the formation of high-energy intermediates. As a result, ultrasound is an effective method for the rapid and efficient synthesis of a wide range of heterocycles and fused heterocycles. Ultrasonic-assisted organic synthesis (UAOS) is a powerful, green approach that is increasingly employed to accelerate the synthesis of organic compounds. Additionally, it has significant applications across various industries, including chemical synthesis, pharmaceuticals, food, polymers, electroplating, and decontamination. Compared to conventional methods, ultrasound-assisted synthesis is more convenient, offering higher yields, shorter reaction times, milder conditions, and easier control [27].

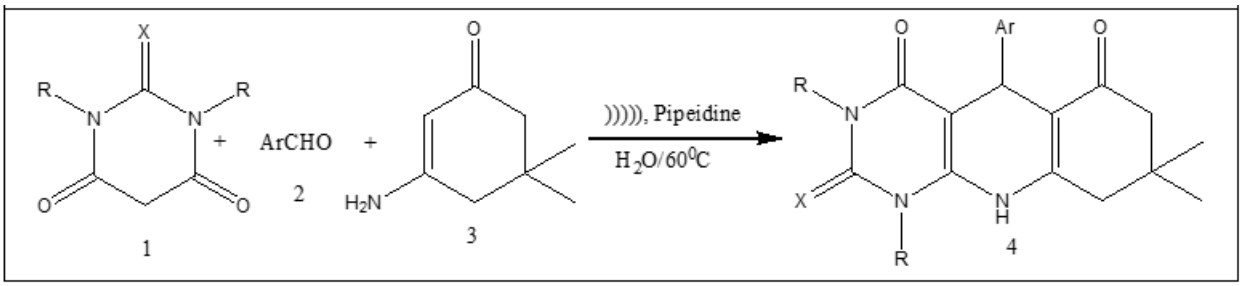
Below, several specific applications of ultrasound-assisted synthesis are described as follows.

Mosslemin et al. [28] reported a one-pot, three-component condensation reaction of barbituric acid **1**, aromatic aldehyde **2**, and enamine **3** in the presence of piperidine and water under ultrasonic irradiation at 60°C to give the desired pyridodipyrimidines **4** in good yields (Scheme 12).



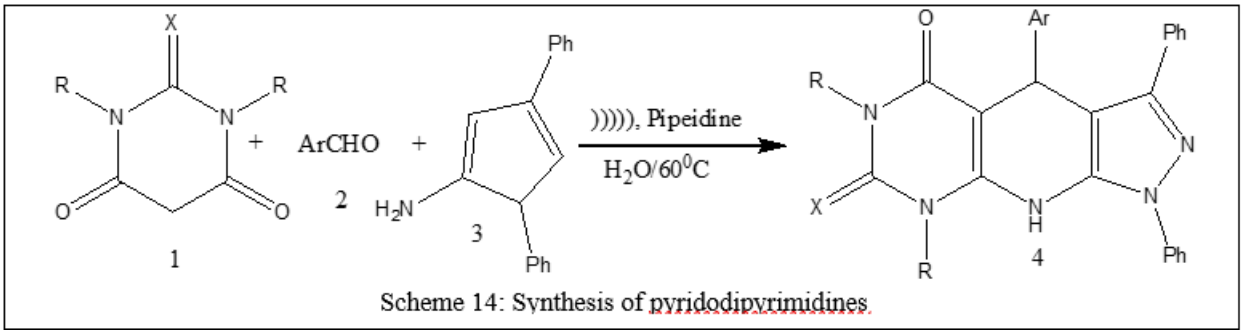
Scheme 12: Synthesis of pyridodipyrimidines

The same authors also synthesized pyridopyrimidines **4** with equal effectiveness under ultrasonic irradiation at 60°C by reacting barbituric acid **1**, aromatic aldehyde **2**, and aminocyclohex-2-enone **3** (Scheme 13).



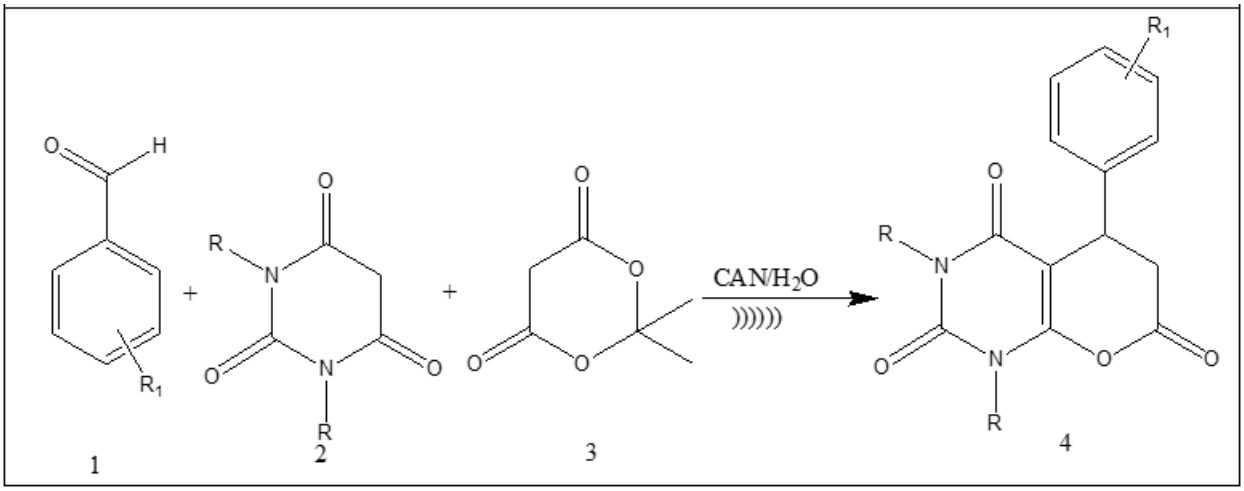
Scheme 13: Synthesis of pyridodipyrimidines

The reaction was also conducted using barbituric acid **1**, aromatic aldehyde **2**, and pyrazole 3, resulting in the formation of pyrazolo pyridopyrimidines **4** under ultrasonic irradiation, achieving good yields (Scheme 14).



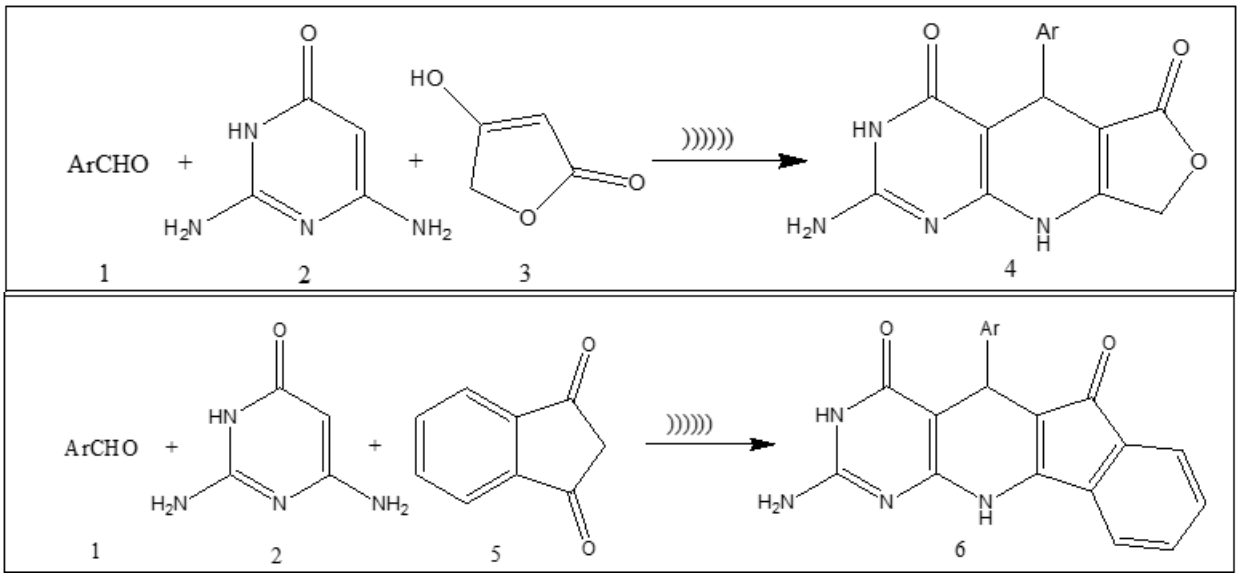
Scheme 14: Synthesis of pyridodipyrimidines

Anshu et al. [29] employed ceric ammonium nitrate (CAN) as an efficient catalyst for synthesizing pyrano[2,3-d] pyrimidine-2,4,7-triones **4** in an aqueous medium under sonication. This was achieved through a one-pot, three-component reaction involving benzaldehyde **1**, barbituric acid **2**, and Meldrum's acid **3**, conducted at 50% power of the processor and in a 4-s pulse mode until the solid product separated. The completion of the reaction was monitored by TLC, using n-hexane:ethyl acetate (7:3) as the eluent. All reactions were completed within 25–40 minutes (Scheme 15).



Scheme 15: Synthesis of pyrano[2,3-d]pyrimidine-2,4,7-triones

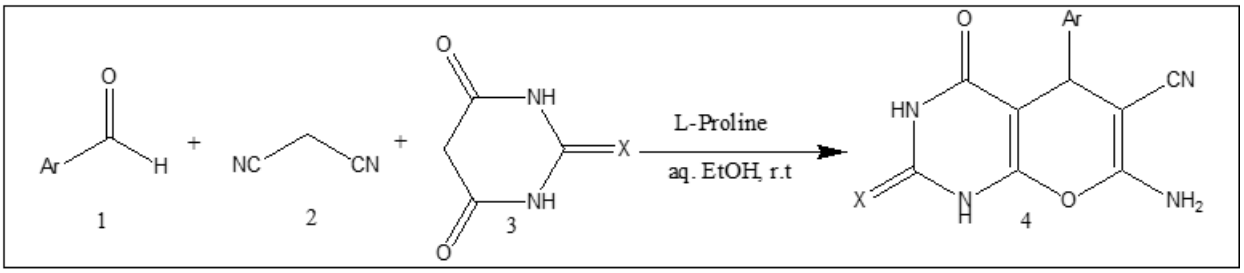
Shujiang et al. [30] reported the synthesis of a series of pyrido[2,3-d]pyrimidine derivatives (**4 & 6**) and related compounds through the condensation reaction of aromatic aldehyde **1**, 2,6-diaminopyrimidine-4(3H)-one **2**, and eithertetronic acid **3** or 1,3-indanedione **5**. This reaction was carried out under ultrasonic irradiation in an open vessel at 65°C, with the reaction time lasting 20–45 minutes until the starting material disappeared, and no catalyst was used. This method offers advantages such as higher yields, lower cost, and a more convenient procedure (Scheme 16).



Scheme 16: Synthesis of a series of pyrido[2,3-d] pyrimidine derivatives

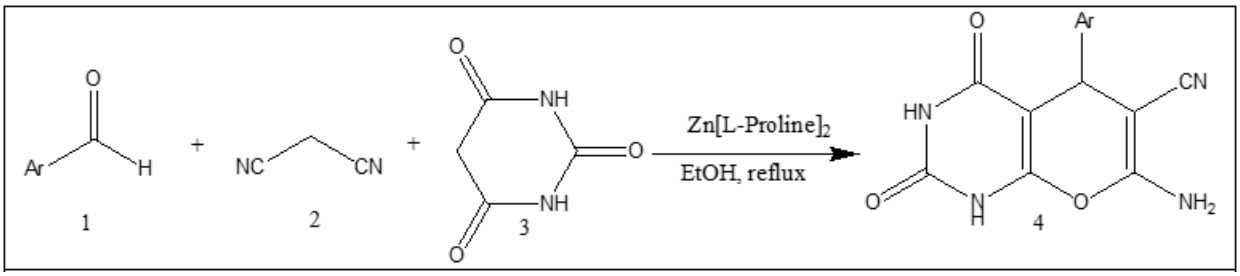
3) Use of Green Catalyst

Bararjanian et al. [31] reported a one-pot synthesis of pyrano [2, 3-d] pyrimidinone derivatives **4** using a mixture of aromatic aldehydes **1**, malononitrile **2**, and barbituric acid/thiobarbituric acid **3**, catalyzed by L-proline in aqueous media (Scheme 17).



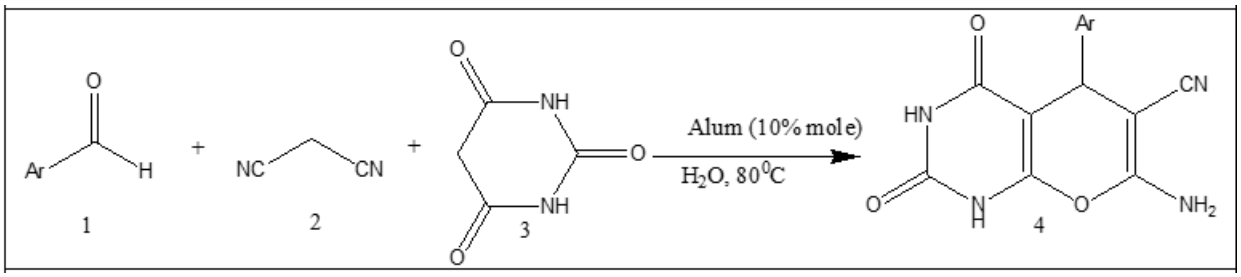
Scheme 17: One-pot synthesis of pyrano [2, 3-d] pyrimidinone derivatives using L-proline

Similarly, Majid et al. [32] reported the synthesis of the same type of product **4** using Zn[(L)proline]$_2$ as an efficient catalyst, with aromatic aldehydes **1**, malononitrile **2**, and barbituric acid **3** as the starting multicomponent reactants (Scheme 18).



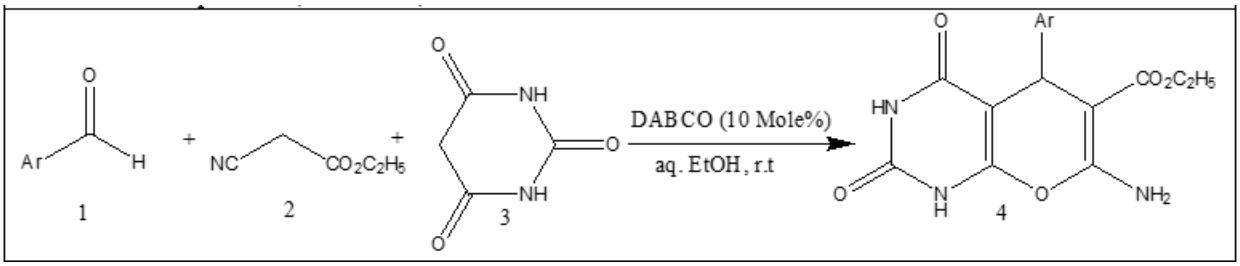
Scheme 18: One-pot synthesis of pyrano [2, 3-d] pyrimidinone derivatives using Zn[(L)proline]$_2$

Akbar et al. [33] reported an environmentally friendly and efficient synthesis of pyrano[2,3-d] pyrimidinone derivatives **4**. This was achieved by using barbituric acid **1**, aromatic aldehyde **2**, malononitrile **3**, and alum (10% mol) as catalysts in water at 80°C (Scheme 19).



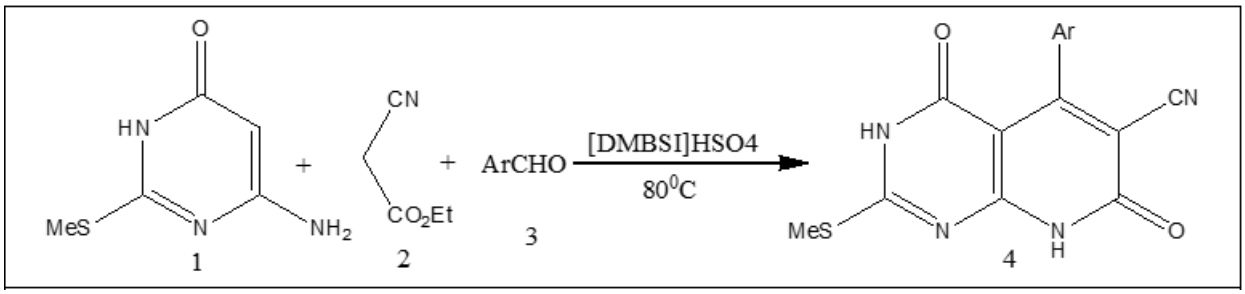
Scheme 19: One-pot synthesis of pyrano [2, 3-d] pyrimidinone derivatives using alum

Bhat et al. [34] reported the synthesis of pyrano [2, 3-d] pyrimidinones **4** through a multicomponent reaction. This involved a solution of aromatic aldehydes **1**, active methylene compound **2**, and barbituric acid **3** (2 mmol each), with 10 mol% 1,4-diazabicyclo [2, 2, 2] octane (DABCO) in a 15 mL mixture of ethanol and water (1:1 ratio). The reaction was stirred for 30–40 minutes at room temperature (Scheme 20).



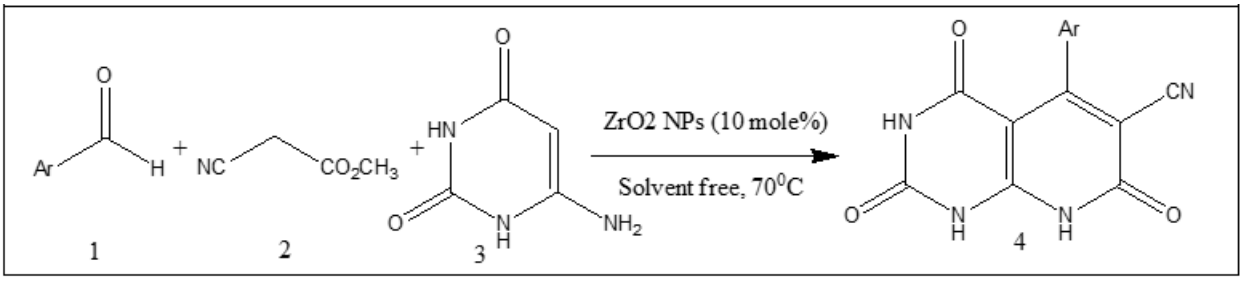
Scheme 20: Synthesis of pyrano [2, 3-d] pyrimidinones using DABCO

Roghayeh et al. [35] reported the one-pot, multi-component synthesis of pyrido [2, 3-d] pyrimidine **4** derivatives using a Brønsted-acidic ionic liquid as a catalyst. A mixture of equimolar amounts of 6-amino-2-(methylthio) pyrimidin-4(3H)-one **1**, ethylcyanoacetate **2** or Meldrum's acid **5**, and aldehyde **3** was added to a vial containing a magnetic stirring bar, along with [DMBSI]HSO$_4$ as the ionic liquid. The reaction was then heated to 80°C (Scheme 21).



Scheme 21: Synthesis of pyrido[2,3-d]pyrimidine derivatives using ionic liquid

Shahrzad et al. [36] reported a simple one-pot synthesis of pyrido [2, 3-d] pyrimidinones **4** by reacting a mixture of aromatic aldehyde **1**, methylcyanoacetate **2**, 4(6)-aminouracil **3**, and ZrO2NPs as a catalyst at 70°C for 1 hour. The organic solution was then poured into cold water (20 mL), filtered, and washed with aqueous ethanol to yield the pure product (Scheme 22).



Scheme 22: Synthesis of pyrido[2,3-d] pyrimidine derivatives using ionic liquid

2. Conclusion

In conclusion, Recent developments demonstrate that microwave and ultrasound assisted multicomponent reactions combined with green catalytic systems provide efficient and environmentally sustainable routes to fused pyrimidine scaffolds. Despite significant advances, challenges remain in mechanistic understanding, scalability, and industrial translation. Future research should prioritize catalyst recyclability, solvent minimization, and integration of computational design strategies to optimize green synthetic pathways for medicinal applications.

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